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NDMA
NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

Better Health Through Responsible Self-Medication

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for Ephedrine, Dihydroetorphine, Remifentanil, and Certain Isomers – Docket 98N-0148, 64 Fed. Reg. 1629, NDMA Comments

Dear Sir or Madam:

On January 11, 1999, the Food and Drug Administration (FDA) published the above-referenced notice requesting comments concerning recommendations by the World Health Organization (WHO) to impose international restrictions, under international treaties, on certain drug substances, including ephedrine. The notice stated this information would be considered in preparing a U.S. position for a meeting of the United Nations (UN) Commission on Narcotic Drugs in Vienna, March 1999.

The Nonprescription Drug Manufacturers Association (NDMA) is the national association representing manufacturers and distributors of nonprescription, or over-the-counter (OTC), medications and dietary supplements. NDMA members account for some 95% of retail sales of OTC medicines in the U.S. NDMA has been active on a number of regulatory, legislative, and international matters affecting ephedrine. NDMA has participated in FDA and Drug Enforcement Administration (DEA) rulemakings; supported precursor control legislation in Congress; and worked with World Self-Medication Industry, the international federation of associations that includes NDMA, to address ephedrine issues.

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Summary.

The U.S. Government should oppose the World Health Organization recommendation that ephedrine be scheduled under the UN Convention on Psychotropic Substances. The WHO recommendation is unsupported, misplaced, and would run counter to well developed U.S. policies. If the UN Commission on Narcotic Drugs nevertheless decides to schedule ephedrine under the UN Convention on Psychotropic Substances over objections, we suggest that the ingredient be subject to a qualified scheduling decision. We also urge the U.S. Government to find that the statutory and regulatory framework in place controlling ephedrine in the U.S. already meets our nation's obligations under the UN Convention.

- Scheduling ephedrine runs counter to established U.S. policies. FDA has already found that ephedrine and certain ephedrine combination drug products are generally recognized as safe and effective when properly labeled for OTC use. Congress and the Drug Enforcement Administration already have a framework in place under three Acts to limit large scale diversion for the manufacture of illicit substances, while maintaining consumer accessibility to legitimate OTC products.

- Concerns expressed by WHO do not establish a sufficient basis for scheduling. The recommendation is based on presumptions, and implies that diversion of ephedrine for use as a precursor chemical is also a factor. This falls short of the type of significant public health problem the Psychotropic Convention is intended to address.

- Concerns expressed by WHO indicate confusion between two different UN Conventions -- the UN Convention on Psychotropic Substances and the UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

- The process used by WHO in making its recommendation lacks the transparency necessary for full and thorough input from interested parties.

- Even if the UN Commission on Narcotic Drugs schedules ephedrine, the Convention permits WHO to recommend and the Commission to adopt qualified scheduling of substances by dosage or form.

- Even if the UN Commission on Narcotic Drugs schedules ephedrine, U.S. laws and regulations concerning ephedrine already meet the obligations the UN Convention on Psychotropics envisions. A UN scheduling decision would still set, however, a dangerous precedent for other legitimate OTC medicines.

- Even if the UN Commission on Narcotic Drugs schedules ephedrine, and assuming, arguendo, that U.S. laws and regulations are not in sufficient accord with UN Convention on Psychotropics obligations, the U.S. framework provides ample cause for an Article 3 exemption.

I. The U.S. Government Should Oppose Scheduling of Ephedrine Under the UN Convention on Psychotropic Substances.

(a) Scheduling ephedrine runs counter to established U.S. policies. Ephedrine has a long and well-established safety and effectiveness record for its intended use as a nonprescription bronchodilator. The FDA Final Monograph on Bronchodilator Drug Products notes that its OTC availability provides asthmatics with ready access to this essential medication without the need for additional visits to a physician's office or to a hospital emergency room.[1] "This availability especially benefits those asthmatics whose attacks are triggered by common environmental factors (primarily exertion, anxiety, exposure to cold, etc.) when immediate use may be essential."[2]

While concerns have been expressed from time to time about ephedrine in nonprescription drug products, at an August 27-28, 1996 meeting of the FDA Food Advisory Committee, a Center for Drug Evaluation and Research official stated that FDA has no reports of significant adverse reactions associated with ephedrine-containing OTCs used for their intended bronchodilator use.[3]

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[1] 51 Fed. Reg. 35326, 35327 (October 2, 1986).
[2] Id.
[3] See FDA Food Advisory Committee transcript, volume II, Wednesday, August 28, 1996, at 116-7 (quoting Dr. Michael Weintraub, Director, Office of Drug Evaluation V, FDA).

FDA has also found ephedrine as generally recognized as safe and effective in appropriate cream, lotion, or ointment to temporarily reduce swelling associated with irritation in hemorrhoids.[4]

NDMA strongly supports the national goal of fighting drug abuse, including opposition to the diversion of legitimate products for use in the production of illicit substances. For example, NDMA supported adoption of the Chemical Diversion and Trafficking Act of 1988, the Domestic Chemical Diversion Control Act of 1993, and the Comprehensive Methamphetamine Control Act of 1996. Many of the specific requirements of these laws, as well as the regulations under them, are described more fully in section III. As a whole, they constitute a thoroughly considered approach to ephedrine control. They demonstrate the intent of Congress to limit diversion of ephedrine for the manufacture of illicit substances, while maintaining consumer accessibility to legitimate OTC products. Congress intentionally did *not* make ephedrine-containing products subject to a controlled substance schedule.

The WHO recommendation to the UN Commission on Narcotic Drugs threatens these decisions made by the Congress and FDA. We urge the U.S. government to oppose the WHO recommendation at the UN Commission on Narcotic Drugs meeting.

(b) Concerns expressed by the World Health Organization do not establish a sufficient basis for scheduling. The WHO assessment criteria under the UN Psychotropic Convention focus on risks and benefits of substances. The specific criteria state –

"Article 2, 4. If the World Health Organization finds:

(a) That the substance has the capacity to produce:

i. (1) A state of dependence, and

(2) Central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behavior or perception or mood, or

ii. Similar abuse and ill effects as a substance in Schedule I, II, III, or IV, and

[4] 21 C.F.R. § 346.12.

(b) That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control, the World Health Organization shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy. . . ."[5]

Further clarifying the type of evidence that triggers a WHO recommendation, the Commentary to the Convention notes that: "It is apparent that only a *significant* health problem appears to be a 'public health' problem as this phrase is used by the Vienna Convention. . . ."[6] As discussed earlier, there have been no official reports nor are we aware of a significant problem with legitimate ephedrine-containing nonprescription medicines in the U.S. FDA, after extensive review, has already found that ephedrine is generally recognized as safe and effective for more than one nonprescription use. The WHO recommendation does not provide sufficient evidence of ephedrine abuse or risks to show a significant public health problem. Rather, the WHO recommendation is far more equivocal. "Ephedrine abuse or illicit traffic in ephedrine *presumably* associated with its abuse," "problem of abuse *seems* to involve ephedrine single entity products," "problem *appears* to be particularly serious in certain African countries" – these are the types of statements WHO uses to describe a perceived problem.[7]

An International Narcotics Control Board (INCB) background paper circulated to some of the WHO Expert Committee members – and evidently the INCB material the WHO recommendation refers to – also provides only inferential links between ephedrine and abuse of the ingredient itself.[8] The INCB background paper discusses unauthorized importation, seizures, and suspicious shipments, but, in the end, it is based on the non sequitur that presence of quantities in excess of those anticipated for expected medical use means the substance itself is

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[5] 1971 UN Convention on Psychotropic Substances, Article 2, 4. (Full citations to the Convention are omitted for the remainder of this submission.)

[6] See Commentary on the Convention on Psychotropic Substances, 1971, United Nations Publication E.76.XI.5, at 46.

[7] See WHO notification on l-ephedrine, and d,l-ephedrine, Reference: NAR/CL.18/1998 CU 98/215, TLAB/CSSS/303/98, UNDCP 42nd CND, WHO/ECDD 31 (1971C), Annex II, at 2-3.

[8] See International Narcotics Control Board background paper for Dr. Cortes-Maramba, fax dated June 22, 1998. (Emphasis added.)

being abused. As discussed below, this conclusion does not necessarily follow, and it confuses the distinction between two different UN Conventions rather than focusing on any public health problem from abuse of the ingredient.

Finally, the WHO recommendation states an ephedrine problem "appears to be particularly serious in certain African countries."[9] Yet at the same time, of the 50 countries returning an ephedrine questionnaire to WHO, 12 indicated some type of problem with ephedrine.[10] Of these 12, only one was an African country.[11] Even if more than one country has *some* degree of a problem, we question whether this qualifies as a widespread health problem that an international agreement such as the UN Convention on Psychotropic Substances is designed to address.

WHO has not presented hard data indicating a public health problem with ephedrine abuse. Lacking such data, the WHO recommendation should be rejected.

(c) Concerns expressed by the World Health Organization indicate confusion between different UN Conventions. The WHO notification on ephedrine notes that a problem of ephedrine diversion was reported in material provided by the International Narcotics Control Board, and that some ephedrine is being used as a precursor to synthesize methamphetamine.[12] The notification goes on to recommend that the interrelationship and interpretation of the 1971 Psychotropic Convention and the 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances needs clarification.[13] We find no basis for considering diversion for production of illicit substances as an assessment criteria under the UN Convention on Psychotropics. The WHO assessment criteria under the Convention clearly focus on the risks and benefits of a ***substance itself***.

Instead, it is the role of the UN Convention Against Illicit Traffic in Narcotic Drugs and Psychoactive Substances to monitor precursors and other chemicals used in the manufacture of

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[9] WHO notification, supra, Annex II, at 2.
[10] Id. (46 of the 50 countries indicated ephedrine was available in their country for medical uses.)
[11] See WHO notification, supra, Annex II, at 2.
[12] WHO notification, supra, Annex II, at 2.
[13] See WHO notification, supra, Annex II, at 3.

illicit substances.[14] We understand that the UN Illicit Traffic Convention does not cover substances in finished pharmaceutical form, and we acknowledge the concern that this provides a means around the UN Illicit Traffic Convention. This type of concern is why NDMA supported the adoption of a number of laws domestically to combat this problem. Sections III and IV describe these U.S. laws. But this does ***not*** provide a rationale for misreading and expanding the scope of the UN Psychotropic Convention.

NDMA would welcome the opportunity to participate in discussions on ways to improve the UN Illicit Traffic Convention. But the UN Psychotropic Convention is, and should remain, focused on abuse of substances themselves, not substances as precursors.

There is also a question of whether a substance can be listed in *both* the UN Illicit Traffic Convention and the UN Psychotropic Convention, or if after a UN Commission on Narcotic Drugs scheduling decision, ephedrine would need to be removed from Table I of the UN Illicit Traffic Convention. If that were the case, in some ways the U.S. would then have *fewer* tools with which to monitor international trade in ephedrine, given the depth of detail on international trade monitoring in the UN Illicit Traffic Convention contrasted with the UN Psychotropic Convention.[15]

(d) <u>The process used by the World Health Organization in making its recommendation did not provide sufficient transparency needed for full and thorough input from interested parties</u>. WHO has prepared "Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control," but the process WHO followed in making this recommendation failed to meet the "principles of openness and

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[14] See UN Convention Against Illicit Traffic in Narcotic Drugs and Psychoactive Substances, 28 I.L.M. 493 (1989). Article 12 in particular focuses on precursors.

[15] See generally, UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Article 12 (9) and (10), describing mandated international trade monitoring systems, including seizure, notification, shipment labeling and documentation, and record retention provisions; and pre-export notification to parties on request. In contrast, Article 11 (5) and (6) of the UN Psychotropic Convention are limited to more general quantity records and record retention for Schedule IV substances. Article 12 on international trade does not apply to Schedule IV substances. Article 13 is limited to country-specific import prohibitions and country-specific special import licenses.

transparency" the guidelines highlight.[16] The guidelines note that information collected by WHO is generally made available for publication, particularly information contained in the report of the WHO Expert Committee on Drug Dependence.[17] While these materials were made available to WHO Expert Committee members, they have *not* been published so that all interested parties could review them. When NDMA questioned WHO on this, we were told "there has not been a policy of publishing these documents for the consumption of the general public, because meetings of WHO Expert Committees are private."[18] This strikes us as the antithesis of the intent of the WHO guidelines, and it falls well short of the fairness and transparency afforded citizens in the U.S. administrative procedure system. If the U.S. government is to develop positions, and if interested parties are expected to have the opportunity for meaningful input into that process, there must be a road map to follow at the WHO level.

Second, at least one document (the INCB background paper discussed above) that meeting observers describe as pivotal was distributed to some but not all committee members and observers. While this document was not prepared by WHO, the facts remain that the WHO guidelines suggest that documents should go to WHO ahead of time and WHO cites material provided by the INCB in its recommendation.[19] WHO, in turn, should then provide such documents, at a minimum, to those attending committee meetings or, more preferably, allow public access to them.

II. Even if the UN Commission Schedules Ephedrine, the Convention Permits WHO to Recommend and the Commission to Adopt Qualified Scheduling of Substances by Dosage or Form.

As discussed above, NDMA believes there are strong reasons to oppose the scheduling of ephedrine under the UN Psychotropic Convention. However, if any scheduling of ephedrine is to occur, the UN Commission on Narcotic Drugs should place on Schedule IV only preparations of ephedrine that are in excess of a specified dosage or in a specified form. For example, NDMA would recommend that the U.S. consider proposing that only ephedrine at greater than 25 mg per

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[16] See "Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control," PND/90.1, at 3, para. 8.
[17] Id.
[18] See letter from Dr. Juhana E. Idänpään-Heikkilä, WHO, to James D. Cope, NDMA, November 26, 1998.
[19] See WHO notification, supra, Annex II, at 2.

dosage unit or in single active ingredient form for oral ingestion (i.e., *not* scheduled in therapeutically useful combination products for oral ingestion at 25 mg or less per dosage unit, or ephedrine sulfate in creams, lotions, or ointments to relieve swelling associated with hemorrhoids) be scheduled under the UN Psychotropic Convention.

We recognize this approach raises the issue of whether the UN Psychotropic Convention permits such qualified scheduling. NDMA concludes the UN Psychotropic Convention permits WHO to recommend and the UN Commission on Narcotic Drugs to adopt such a qualified scheduling decision. In fact, the Convention supports a conclusion that qualified scheduling is required if the adverse effect and risk factors under Article 2 are found inapplicable to certain preparations. This approach would also be consistent with the policy that President Nixon stated in submitting the Convention to the Senate: "the use of psychotropic substances for medical and scientific purposes is indispensable and . . . their availability for such purposes should not be unduly restricted."[20] A limitation by the UN Commission of a scheduled substance to a threshold dosage or particular form is entirely compatible with the authority under Article 3(3) for parties to exempt certain preparations of substances listed under the Convention.

The UN Psychotropic Convention does not contain any definitional provision that is inconsistent with qualified scheduling of ephedrine. Because "substance" is not a defined term, there is no explicit requirement under the Convention that scheduling cover all forms and quantities of a particular chemical. The Convention does define "psychotropic substance" (any substance, natural or synthetic, or any natural material that the Commission adds to Schedules I through IV), and "preparation." But nothing in these definitions expressly precludes WHO from recommending or the UN Commission on Narcotic Drugs from deciding that one or more preparations of ephedrine based on dosage or form be treated as psychotropic substances under the Convention while other preparations, i.e., dosages underneath a threshold or in other forms (e.g., combination products), be excluded from such listing.

The procedure for adding psychotropic substances under the Convention supports permitting qualified scheduling. Article 2(4) of the UN Psychotropic Convention gives criteria

for WHO to determine scheduling is appropriate because a "*substance* has the capacity to produce" certain adverse effects. (Emphasis added.) The WHO assessment of the substance requires weighing a number of factors that may be found entirely inapplicable for a dosage having a particular ingredient below a stated level or in a particular dosage form. Further, Article 2(4) requires WHO to recommend "control measures, if any, that would be appropriate in light of its assessment." All of these factors are consistent with a WHO recommendation that determines that only a molecule in dosages above a specified threshold or in a particular form would have the adverse effects in question or present a risk of abuse. The Convention does not permit scheduling of preparations in dosage or forms that do not satisfy the specified adverse effect and risk factors.

While WHO did not directly address this approach in its notification, WHO did note that ephedrine combination products would be eligible for exemption. This is certainly not inconsistent with a qualified scheduling approach and would achieve the same result.

The UN Commission on Narcotic Drugs also must weigh a number of factors that suggest the appropriateness of qualified scheduling. Article 2(5) requires that the Commission take account of the "economic, social, legal, administrative and other factors" that it considers relevant to adding the "substance" to one of the Schedules. Again, a weighing of these criteria could result in determining that for certain ingredients only dosages above a specified threshold or in a particular form should be scheduled. The open-ended and non-specific nature of these criteria seem to anticipate such qualified scheduling in order to provide a mechanism for factoring into the final outcome the broad considerations set out in Article 2(5).

The exemption procedures under Article 3 of the UN Psychotropic Convention are not inconsistent with this approach. *After* the Commission has listed a psychotropic substance, Article 3 permits a party to determine that one or more of its preparations present no or negligible risk of abuse or of recovery of the substance in a quantity liable to abuse. The party may then notify WHO that such preparations are exempted in its territory or region from some of the requirements under the Convention.

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[20] Letter of Submittal (June 18, 1971), "Convention on Psychotropic Substances," Executive G, 92nd Cong., 1st

Article 3 contains no language suggesting that such subsequent exemption of certain preparations of ephedrine would in any way preclude WHO from recommending *initially* or the Commission from adopting *initially* a qualified scheduling of ephedrine based on dosage or form. Meanwhile, parties are always free as a matter of domestic law to require that industries comply with some aspects of Convention requirements for substances that fall outside the scope of a qualified scheduling decision.

If the Commission were to adopt a qualified scheduling approach discussed here, there is less likely to be any controversy regarding party exemptions for particular preparations. Further, this approach potentially avoids or minimizes having to deal with the complex issues raised by any disagreement over national exemptions for preparations that can lead to invocation of Article 3(4) of the Convention.

It is true that WHO and the UN Commission on Narcotic Drugs have to date not taken this approach in previous scheduling decisions under the UN Psychotropic Convention. But the Convention should always be interpreted to take account of the future needs of the international community. Ephedrine is especially suitable for a qualified scheduling decision and is not an active ingredient that should be listed under the 1971 Convention regardless of dosage or form. Ephedrine is precisely the type of chemical President Nixon was referring to when he pointed out that the less extensive controls of the UN Psychotropic Convention were necessary because "the world community has had a century of experience in the application of international controls to narcotic drugs . . . and has had no experience with respect to the psychotropic substances."[21] The UN Psychotropic Convention should not be interpreted to impose a requirement for scheduling that is excessively restrictive, i.e., covering all forms of a chemical, when such over-inclusive scheduling is not, as shown here, required by the Convention's provisions.

Sess. (June 29, 1971).
[21] Id. at VII.

III. Even if the UN Commission on Narcotic Drugs Schedules Ephedrine, U.S. Laws and Regulations Concerning Ephedrine Already Meet the Obligations the UN Convention on Psychotropics Envisions.

FDA notes that ephedrine is a listed chemical under the Controlled Substances Act and is subject to regulations enforced by the Drug Enforcement Administration.[22] The agency states these controls must be examined to determine whether they enable the U.S. to fulfill its Convention obligations, assuming ephedrine is so scheduled.[23] While NDMA urges the U.S. government to oppose or defer scheduling by the UN Commission on Narcotic Drugs, the association also believes the U.S. framework does indeed meet the obligations envisioned by the UN Convention on Psychotropic Substances.

NDMA supported adoption of the Chemical Diversion and Trafficking Act of 1988, the Domestic Chemical Diversion Control Act of 1993, and the Comprehensive Methamphetamine Control Act of 1996 (CMCA). These laws were enacted to help combat the diversion of precursor chemicals, including ephedrine, to clandestine methamphetamine production. DEA has extensive powers under the three Acts to address diversion at all levels, including against rogue companies operating at the fringes of legitimate commerce that import bulk precursor chemicals, formulate them into dosage units, and distribute those units in large quantities to persons engaged in methamphetamine production.[24]

The provisions of the CMCA:

- Make the possession of list I chemicals a crime in instances where the chemicals were obtained under a registration that was suspended or revoked.
- Extend federal "long arm" jurisdiction for certain controlled substance offenses to include the manufacture and distribution of listed chemicals outside the U.S. with intent to illegally import them.

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[22] 64 Fed. Reg. 1629, 1633 (January 11, 1999), citing 21 U.S.C. 802(34) and 21 CFR 1309, 1310, and 1313.
[23] 64 Fed. Reg. 1629, 1633 (January 11, 1999).
[24] DEA has noted the CMCA replaces rules by DEA in this area with a more comprehensive system of controls relating to distribution, importation, and exportation of combination ephedrine products (single ingredient ephedrine products were already covered) and two other nonprescription drug ingredients, along with other strong tools to attack illicit diversion. See 62 Fed. Reg. 52294 , 52296 (October 7, 1997).

- Establish higher maximum penalties for the manufacture, import, export, possession or distribution of chemicals or equipment used in methamphetamine production (10 years for a first offense and 20 years for a subsequent offense). The law also directs the sentencing commission to review and amend sentencing guidelines for methamphetamine offenses and to enhance penalties for offenses involving list I chemicals.

- Impose a civil fine of up to $250,000 for any firm which distributes a laboratory supply to a person who uses it in a clandestine lab, where the distribution is with "reckless disregard" for the intended illicit use.

- Enhance the Attorney General's injunctive authority and establishes new injunctive authority relating to various violations of the Controlled Substances Act, including certain violations relating to listed chemicals and other chemicals, products, and equipment used in the manufacture of controlled substances.

- Include provisions for the restitution of cleanup costs by a defendant convicted of offenses involving clandestine methamphetamine labs.

- Establish advisory panels and task forces to evaluate methamphetamine education and prevention programs, to monitor methamphetamine abuse within the U.S., and to develop programs to aid industry in better identifying suspicious orders.

- Subject ephedrine-combination products to a 24 gram, single-transaction limit for registration, recordkeeping, and reporting under the Controlled Substances Act (single ingredient ephedrine products were already covered). DEA has issued an interim rule temporarily exempting retail distributors of ephedrine-combination products from the registration requirements for single transaction sales below 24 grams of ephedrine base, and has issued a proposed rule to make the exemption permanent.

- Mail order distributors must report to DEA all sales of ephedrine (and two other nonprescription drug ingredients) to "non-regulated" persons on a monthly basis.

We believe that these types of controls meet, and in some cases exceed, U.S. obligations under the UN Convention on Psychotropics even if ephedrine were scheduled by the UN Commission on Narcotic Drugs. To review some of those obligations, comparing the current U.S situation to the relevant UN Convention article --

Article 8 -- Licenses: Manufacturers, wholesalers, and distributors already need to register (the U.S. license equivalent), except for a temporary exemption (proposed as permanent) for retail distributors for single transaction sales below 24 grams of ephedrine base. Beyond that, it is unclear whether "distribution" in Article 8 is intended to apply at the retail sales level, as opposed to the wholesale distribution level. Since Article 9, discussed below, specifically refers

to supply for use by individuals and retail distributors, the implication is that Article 8's open-ended "distribution" reference is focused on the wholesale distribution level. If so, U.S. mail order requirements and the existence of *any* retail threshold exceed our UN Psychotropic Convention obligations.

Article 9 -- Prescriptions: It is true that the current framework for ephedrine does not require that it be supplied only with a medical prescription, as the UN Convention on Psychotropics would suggest. But the UN Convention provides authority for a party to allow pharmacists or other retail distributors to supply, without prescription, Schedule IV substances in small quantities. Further, Article 5, paragraph 3 notes that it is "desirable" -- not mandatory -- that parties do not permit possession of Schedule IV substances except under legal authority. DEA's 24 gram single transaction sales exemption meets the thrust of the UN Convention's intent, particularly since, going beyond the UN Convention, U.S. retailers have a duty to report "suspicious transactions" of ephedrine even apart from the 24 gram exemption rule and since wholesalers and distribution centers are subject to registration and record-keeping requirements. In addition, nine individual states require retailers to register or obtain a permit to sell nonprescription medicines (including ephedrine-containing products), and a 10th state requires retailers receiving shipments of certain nonprescription medicines from outside of the state to register.

Article 10 -- Package Warnings, Advertising: Nonprescription medicines containing ephedrine already include label information needed for safe use of the product. As to advertising, the UN Convention notes constitutional considerations must be taken into account. It does not mandate an advertising prohibition. (Indeed, it could not – a discussion well beyond the subject of FDA's notice.)

Article 11 -- Records: Manufacturers, exporters, and importers are already subject to record-keeping requirements. For that matter, so are distributors and retailers exceeding the single transaction 24 gram exemption – requirements beyond the UN Convention.

Articles 12 and 13 – Import and Export Registration and Requirements: .Current U.S. law already imposes registration requirements for importers and exporters of ephedrine. Even if adopted, the WHO recommendation to place ephedrine in Schedule IV would not require the U.S. or any other party to impose import/export control requirements. Article 12 imposes certain export control and/or import/export declaration requirements only for substances listed under Schedules I, II, and III of the Convention, not Schedule IV. Further, existing U.S. law provides ample authority for export requirements in the event that a party notifies WHO under Article 13 of the Convention that the state is prohibiting imports of a Schedule IV substance. There is also the question of what would happen if scheduling ephedrine in the UN Psychotropic Convention resulted in its removal from Table I of the UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, since the latter has more detailed provisions on international trade (as discussed earlier on page 7).

Article 15 – Inspection: Under existing federal and/or state law, manufacturers, exporters, importers, and wholesale and retail distributors are subject to inspection by government authorities.

Article 22 -- Penal Provisions: Ephedrine is already subject to the types of considerations expressed in this Article.

One might wonder, if the existing U.S. framework satisfies the Convention, why NDMA cares whether or not ephedrine is scheduled. The answer is straight-forward: Scheduling ephedrine would set a dangerous precedent for future UN Commission on Narcotic Drugs scheduling decisions. If a legitimate OTC drug such as ephedrine – with no record of abuse in the U.S. to justify treatment as a controlled substance – is scheduled under the Convention, other legitimate OTC drugs could be targeted in the future.

Finally, a finding that the U.S. framework controlling ephedrine meets our UN Psychotropic Convention obligations would be in line with Congress' intent in the Comprehensive Methamphetamine Control Act of 1996: Continued consumer accessibility to these products remains an important objective. Congress did *not* make ephedrine-containing products subject to a controlled substance schedule requiring a prescription.

IV. Even if the UN Commission on Narcotic Drugs Schedules Ephedrine, and Assuming, Arguendo, that U.S. Laws and Regulations Are Not in Sufficient Accord with UN Convention on Psychotropics Obligations, the U.S. Framework Provides Ample Cause for an Article 3 Exemption.

As described in section III, the U.S. framework to control ephedrine is quite extensive. While NDMA hopes the UN Commission on Narcotic Drugs will not schedule ephedrine and while we urge the U.S. government to oppose scheduling, *if* ephedrine is scheduled and *if*, contrary to our position, there is reason to think that the existing U.S. framework for ephedrine does not meet our UN Psychotropic Convention obligations, then in the alternative we would urge the U.S. to notify the UN of an Article 3 exemption for legitimate ephedrine products in the U.S.[25] This is particularly true given the discussion of above of the existing U.S. framework vis-à-vis Articles 8, 11, 13, 15, and 22.

In making its ephedrine recommendation, WHO notes that ephedrine combination products would be eligible for exemption under the Convention.[26] We believe other approaches are preferable to an exemption. However, given that we are not aware of data to question the safe and effective approved uses of ephedrine, we would argue in the alternative that nonprescription ephedrine combination products, or nonprescription ephedrine in dosage forms such as creams or ointments for hemorrhoids, meet the exemption grounds of Article 3 of the UN Psychotropic Convention. They are made in such a way as to present a negligible risk of abuse. In addition, given the DEA's 24 gram retail limitation on single transactions of ephedrine-containing products without triggering registration, recordkeeping, and reporting requirements, Article 3's direction that quantities liable to abuse not be exempted would also be met.

V. Conclusion.

A decision by the UN Commission on Narcotic Drugs to schedule ephedrine under the UN Convention on Psychotropic Substances would run counter to U.S. policies. The WHO notification making this scheduling recommendation is flawed: it does not provide hard data for

[25] The Article 3 exemption route would involve an increased administrative burden on the U.S. government, as manufacturers of ephedrine-containing products filed for exemptions. Such a burden would be continuing as the marketplace evolves and new products are introduced. In addition, if the UN were to schedule, a precedent would be set for other OTC ingredients with markets orders of magnitude larger than the OTC ephedrine market.

[26] See WHO notification, supra, Annex II, at 3.

its recommendation; it confuses the roles of two different UN Conventions; the process under which it was developed suffers from a lack of transparency. The U.S. government should actively oppose the scheduling of ephedrine at the UN Commission on Narcotic Drugs meeting in March in Vienna.

If, however, the UN Commission on Narcotic Drugs schedules ephedrine in any event, a Commission scheduling decision could be qualified to exempt legitimate, ephedrine-containing combination products or ephedrine non-ingested dosage forms. Alternatively, we encourage the U.S. government to find that the existing U.S. framework for ephedrine meets our Convention obligations; or notify the UN of an exemption under Article 3 of the UN Psychotropic Convention.

Thank you for considering our views.

Sincerely,

David C. Spangler
Vice President - International
& Assistant General Counsel

cc: Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA
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